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10/663,693	09/17/2003	Evgenu Nudler	NUDLER2A	3974

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EXAMINER	
SACKEY, EBENEZER O	
ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/663,693	NUDLER ET AL.	
	Examiner	Art Unit	
	EBENEZER SACKEY	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 9-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-14,21,22 and 24-26* is/are rejected.

7)☒ Claim(s) *28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/01/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-7 and 9-27 are pending.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9-14, 21-22 and 24-26 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons set forth in the previous office action mailed on 06/06/08.

Response to Amendment/Remarks

Applicant's arguments filed 12/01/08 have been fully considered but they are not deemed persuasive. Applicants argue that the term “perfluorocarbon” appearing in the claims is a term of art. The Examiner agrees and therefore has withdrawn the rejection based on the use of the term. Applicants have provided a series of articles asserting the correlation levels of nitric oxide to a variety of disease state. However, none of the articles account for the various mechanisms which is attributed to the etiology of for example the various cancers or various inflammatory conditions or various microbial bodies, be it bacteria (gram positive or gram negative), fungi or viruses that exist.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9-14, 21-22 and 24-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims rejected herein embrace for example all types of cancers for method claims 1-7 and 26 and additionally cover all viruses at the very least for claim 24 as determined by a reading of the specification . Applicants urge that the "PTO no longer rejects for undue breadth…" but this is quite incorrect. At the very least MPEP 2164.03 considers such a rejection proper in unpredictable art areas such as present in the instant case. Also see the PTO website <<http://www.uspto.gov/web/offices/pac/dapp/1pecba.htm#7>> ENABLEMENT DECISION TREE, Example F, situation 1) which is directed to the scope of cancers. Also, contrary to what applicants state, known NO inhibitors having undergone more testing than reported herein are not reported as viable for the treatment of any and all cancers, much less any particular virus, despite what appears to be their protective role in some diseases. See Neil Hogg article provided by applicants which says *S*-Nitrosothiol compounds *appear to play a role* in signal transduction and stress responses and thus, these compounds have a multitude of pharmacological effects. Note that is far from acknowledging the inhibition of a specific disease. None of the cited show a small number of cell lines which can be tested for leukemia (claim 26) in any variation for cytotoxicity and thus, for reasonable assurance/predictability as to what

other types of cancers instant compounds can inhibit cell growth. Additionally, cell line testing is not a reliable guide for *in vivo* treatment since such testing has historically failed to produce a proportionate number of compounds having a wide spectrum of tumor activity. In the case of brain cancers alone, such a test is meaningless since it does not (and can not) determine if the compound can pass through the blood-brain barrier. Thus the testing described in the specification is not remotely commensurate with the literally hundreds of type of cancers affecting different organs (anal, bladder, breast, cervical, esophageal, eye, blood, liver, larynx, gallbladder, ovary, kidney testes, thyroid, brain, etc. and many different types for each) that is covered by the claim language even if test data was reported in the specification although none is present only description of testing type as emphasized in the previous action. While the level of skill in the cancer art may be high for some cancers it is an unfortunate fact that many types are intractable- gliabastomas, mouth, liver, metastatic melanoma and many others. Thus overall it cannot be said that the level of skill is high. Note *In re Fisher* 166 USPQ 18 previously cited. Also, note MPEP 2164.08(b) which states that claims that read on "... significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative." . Clearly that is the case here.

Claims 1-7 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Such a utility cannot be deemed enabled. .

Pursuant to In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see In re Vaeck, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds.

(b) Scope of the diseases covered. As noted above, the scope of autoimmune disorders is unclear.

The "autoimmune diseases" are processes that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There are dozens of such diseases, which have fundamentally different mechanisms and different underlying causes. Known autoimmune disorders, or disorders generally considered to be

autoimmune include Polymyositis, Scleroderma, Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), Meniere's disease, Omenn syndrome, Idiopathic neutropenia, Idiopathic thrombocytopenic purpura, Autoimmune hemolytic anemia, Premature ovarian failure, Idiopathic hypoparathyroidism, primary biliary cirrhosis, Pemphigus, multiple sclerosis, autoimmune uveitis, rheumatoid arthritis, Addison's disease, Silent thyroiditis, atrophic gastritis, myasthenia gravis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, hemolytic anemia, systemic lupus erythematosus, Wegener's granulomatosis, polyarteritisnodosa, erythema nodosum leprosum, Guillain-Barré syndrome (GBS), allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss (IPBSNHL), aplastic anemia, pure red cell anemia, polychondritis, Stevens-Johnson syndrome, Alopecia areata, asthma, idiopathic sprue, lichen planus, Crohn's disease, Graves ophthalmopathy, sarcoidosis, primary biliary cirrhosis, type I diabetes, autoimmune optic neuritis, uveitis posterior, or interstitial lung fibrosis, Reiter's syndrome, Sjogren's Syndrome, Goodpasture Syndrome, inflammatory bowel disease, Essential Mixed Cryoglobulinemia, Behçet's Syndrome, Chronic Inflammatory Polyneuritis (CIPD), CREST Syndrome, Antiphospholipid Syndrome, Relapsing Polychondritis (systemic chondromalacia or von Meyenburg disease), Retroperitoneal Fibrosis, Celiac disease, Vitiligo, “immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome” (IPEX), Autoimmune Atherosclerosis and many more.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information provided . Further, it is completely generic. That is, it is the same dosage for all disorders listed in the specification, which is a very substantial range of disorders.

(4) State of the Prior Art:

(5) Working Examples: There are no working examples to the treatment of any actual disorder. There are some biochemical tests,

(6) Skill of those in the art: This very much depends on the particular art area.

I. There are both chronic and acute "autoimmune diseases", most of which lack satisfactory treatment. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task. In fact, there are four basic mechanisms underlying autoimmune disease: 1. Antibody mediated diseases: a specific antibody exists targeted against a particular antigen (protein), which leads to its destruction and signs of the disease. Examples are: auto-immune mediated hemolytic anemia, where the target is on the surface of the red blood cell; myasthenia gravis where the target is the acetylcholine receptor in the neuromuscular junction; hypoadrenocorticism (Addison's) where the targets are the cells of the adrenal gland. 2. Immune-complex-mediated diseases: antibodies are produced against proteins in the

body. These combine into large molecules that circulate around the body. In systemic lupus erythematosus (SLE) antibodies are formed against several components in the cell's nucleus (hence the anti-nuclear antibody test (ANA) for SLE). Most notably antibodies are made against the body's double stranded DNA, and form circulating soluble complexes of DNA and antibody, which break down in skin causing an increased sensitivity to ultraviolet light and a variety of signs. As the blood is filtered through the kidneys, the complexes are trapped in the glomeruli and blood vessels, causing the kidney to leak protein - glomerulonephritis. They also cause leakage in other blood vessels, and there may be hemorrhaging, as well as accumulating in synovial fluid and causing signs of arthritis and joint pain. Rheumatoid arthritis results from immune complexes (IgM class antibody called rheumatoid factor) against part of the patient's own immune system (part of its IgG molecules). These form complexes that are deposited in the synovia of the joint spaces causing an inflammatory response, joint swelling, and pain. The collagen and cartilage of the joint breaks down and is eventually replaced by fibrin which fuses the joints - ankylosis. 3. Antibody and T Cell-mediated diseases: T cells are one of two types (the other being B-cells), which mediate immune reactions. Upon exposure to a particular antigen, they become programmed to search for and destroy that particular protein in future. Once a patient has been exposed to an antigen, he will be able to mount a much faster response to it the next time it encounters it. This is the basis of vaccination. Thyroiditis (autoimmune hypothyroidism) seems to be of mixed etiology. Several target antigens have been identified, including thyroglobulin the major hormone made by the thyroid. Auto-

antibodies to antigens in the epithelial cells of the thyroid have also been found. The thyroid becomes invaded by large numbers of T and B cells as well as macrophages, which are cells that engulf and destroy other cell types. T cells specifically programmed for thyroglobulin have been identified. Autoimmune disorders can arise from the killer T-cells, from the helper T-cells, or from the regulatory T-cells (e.g. IPEX syndrome). 4. Diseases arising from a deficiency in complement: When an antigen and antibody react they may activate a series of serum enzymes (the complement system) whose end result is either the lysis (breakup) of the antigen molecule or to make it easier for phagocytic cells like the macrophages to destroy it. Patients with deficiencies in enzymes activated early in the complement system develop autoimmune diseases like SLE. Thus, with such differing mechanisms, it is not logical that a treatment for autoimmune diseases generally can be found.

II. Autoimmune disorders are among the most complex and difficult to understand of all major categories of human disease. An example of this is scleroderma, which kills thousands of Americans every year. It is not even clear if the disorder is best understood as a vascular disease, a fibrotic disease, or an immune disease. Its cause—or causes—remains murky. Its molecular mechanisms or genetic origins have never been nailed down. Partially as a result, no compound has ever been established as effective in treating the disorder itself. While anti- TGF- b drugs have been given to reduce fibrotic scars, and ACE inhibitors provided to protect the kidneys, and still others are given to combat pulmonary hypertension, none of these combat scleroderma itself. While some general immunosuppressive drugs showed promising results even in Phase

II studies, as of the filing date, and even now, none have ever been established as effective against scleroderma.

III. IBD is a generic term for an entire family of disorders, the most important of which are Ulcerative colitis and Crohn's disease. Less common forms include lymphocytic colitis, collagenous colitis, Ischaemic Colitis, Behçet's Syndrome, and Infective Colitis. IBD arises from a range of causes, known and unknown. Ulcerative colitis, Behçet's Syndrome and Crohn's disease, for example are idiopathic.

IV. Autoimmune neuritis is any inflammation of the nerves arising from the body's own immune system, and includes Guillain-Barre Syndrome and Miller Fisher Syndrome. GBS is often preceded by a viral or bacterial infection, surgery, immunization, lymphoma, or exposure to toxins. Demyelination occurs in peripheral nerves and nerve roots, and weakness of respiratory muscles and autonomic dysfunction may occur. Miller Fisher Syndrome involves oculomotor dysfunction, ataxia, and loss of deep tendon. The ataxia is produced by peripheral sensory nerve dysfunction. Facial weakness and sensory loss may also occur. The process is mediated by auto antibodies directed against a component of myelin found in peripheral nerves. GBS and Miller Fisher Syndrome are both quite refractory. Conventional immune suppressant drugs such as methylprednisolone have not been effective, and so the skill level in these disorders is low. Only plasma exchange therapy and intravenous immune serum globulin (IVIG) have proven effective.

Examples of pharmaceutically untreatable autoimmune disorders include celiac disease, APECED, scleroderma and ALS. Medicines can be given to relieve symptoms,

e.g. replace missing hormones, combat pulmonary hypertension or ameliorate pain, but these pharmaceuticals do not treat the disease itself.

(7) The quantity of experimentation needed: Especially in view of points 1, 4, 5 and 6, the amount is expected to be high.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Scleroderma from http://www.sciencemag.org/cgi/reprint/322/5902/667.pdf

With respect to inflammation, firstly, for a compound or genus to be effective against all the diseases listed is contrary to medical science. "Inflammation" for example, is a process that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, leukotrienes, cytokines, and many, many others. Accordingly, treatments for diseases associated with inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against all inflammation related diseases generally.

Inflammation is the reaction of vascularized tissue to local injury; it is the name

given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages that have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

5) Amount of direction and guidance provided by the inventor.

No specific amount of guidance is provided, which would embraces a myriad of conditions and thus, bridge the gap between *in vitro* activity and *in vivo* utility, which is

large enough to warrant thorough and compelling *in vivo* or clinical data.

6) Existence of working examples.

As discussed above, no working example wherein *in vitro* activity can be ascertained.

7) Breadth of claims.

Diseases in claim 1 is extremely varied due to the various pathways and mechanisms involved.

8) Level of ordinary skill in the art.

The level of ordinary skill in the art is high. Due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Hence, the specification fails to provide sufficient support of the broad use of the compounds of the claims for the treatment of the various diseases listed. Thus, necessitating one of ordinary skill in the art to perform an exhaustive search to determine which diseases can be treated by what compounds of the instant claims in order to practice the claimed invention.

Genentec Inc. V. Novo Nordisk A/S (CAFC) 42 USPQ 2D 1001, states that:

"a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors, and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of ordinary skill in the art

would have to engage in undue experimentation to test which diseases can be treated by the compounds encompassed in instant claims, with no assurance of success.

The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms, and treatment (or lack thereof) for the various diseases. It establishes that it is not reasonable to any agent to be able to treat all of the various diseases generally.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are of indeterminate scope since the metes and bounds of “nitrosative stress” and "regulating perturbations in interactions between local and systemic bond remodeling” cannot be ascertained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to EBENEZER SACKEY whose telephone number is (571)272-0704. The examiner can normally be reached between the hours of 7.30 am - 4.30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624

EOS